# EDITORIALS

## Rational Drug Therapy in Patients with Renal Disease

WILLIAM BENNETT'S PAPER in this issue of the JOURNAL is a welcome and scholarly review of the important topic of drug therapy for patients with renal failure. It will be a difficult article for many physicians to read simply because few clinicians have a working knowledge of the pharmacokinetic formulae presented and consequently may become bogged down by the equations. This is unfortunate because the concepts presented, as well as the principles discussed, should help us to practice better therapeutics. The physician who has difficulty with the article should refer to an explanatory background discussion of these concepts, presented without mathematical detail, that appeared in the *British Medical Bulletin* (27:142-147, 1971).[1]*

The value of understanding the role of the kidney in the pharmacokinetics of drugs stems from its practical importance. Briefly and simply, the role of the kidney in drug kinetics parallels its normal physiologic activities; namely, drug excretion is influenced by filtration, passive transport and active transport. Reduction in filtration for the most part relates directly to reduced drug excretion, if no compensatory mechanisms exist (such as increased hepatic metabolism).[2] The decreased excretion of digoxin and the aminoglycoside antibiotics in azotemia are probably the best known examples of diminished filtration.[3,4] Passive reabsorption is largely dependent on passive, nonionic diffusion; a substance more readily passes through a lipid membrane if it is not ionized, rather than ionized. This phenomenon is clinically important for drugs that are weak acids or weak bases.[5,6] The enhanced excretion of weak acids, such as salicylates and phenobarbital when the urine is alkaline, and diminished excretion of weak bases, such as quinine, amphetamine and ephedrine, underscore the clinical importance of this concept.[7-9] Bennett states that drugs that are most susceptible to this phenomenon have pKa (the pH at which the drug is in equilibrium between the ionized and nonionized state) values in the range of 5.0 to 8.0, but reabsorption of drugs of lower or higher pKa may be affected by small changes in urinary pH. The active tubular transport of drugs is exemplified by the use of probenecid to compete for active renal tubular secretion of penicillin, thereby prolonging its effects. Other drugs, including phenylbutazone, sulfinpyrazone, indomethacin and salicylates, compete for these same pathways and may have clinically important effects on each other's excretion.[10]

For many drugs, the clinical significance of changes in renal function to their administration is unknown. For others, theoretic considerations predict importance, but the appropriate clinical studies have not been published. The importance of *clinical* studies for verification or repudiation of the theoretic expectation must be emphasized. The various formulae provided for calculation of dose or dose interval in patients with renal failure may not be sufficient for all patients. Observed levels of drug may differ from those predicted by a formula or nomogram. Even sophisticated computer programs for estimation of digoxin dosage perform better when given an individual patient's serum level of drug.[11] Further, these formulae do not consider the possibility that, in uremia, alterations in drug metabolism may occur. The importance of clinical studies is also relevant to dialysis in poisoned patients. The decision to dialyze is not based solely on the amount of drug that can be removed, but rather on whether or not clinical studies show that the patient has a better prognosis with dialysis than with conservative management.

Whether to give a patient with azotemia a constant dose of antibiotics at larger dosing intervals, or a reduced dose at constant dosing intervals, is currently being debated. Advocates of the latter approach point out that levels of drug in the serum fluctuate less with small doses at conventional intervals.[1] If a relatively constant level promotes efficacy and diminishes toxicity, this method is clearly preferable. A study comparing these alternatives with gentamicin has shown the

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reduced dose-constant interval method is superior in extremely ill azotemic patients.[12] The results of this study cannot be extrapolated to all antibiotics, but do point out the value of appropriately designed patient studies.

The lack of clinical studies, the limited availability of determinations of serum levels of drugs and the multiple theoretical ways in which drug kinetics could be altered in renal failure may leave a practicing physician unsure of what to do in an individual patient. His primary recourse must and should always be clinical endpoints. The possibility of abnormal kinetics should alert clinicians to signs and symptoms that may indicate either toxicity or lack of efficacy. He can follow serum minimum inhibitory concentrations of an antibiotic one hour after a dose and just before the next; he can look at frequent electrocardiographic rhythm strips of a patient who is taking digoxin; and he can check electrocardiograms of a patient who is taking procainamide (and thus determine lack of efficacy or signs of toxicity). The important points are that the clinician must be aware of the potential for abnormal kinetics in renal failure, he must know the pharmacology of the drugs he selects and he must follow clinical endpoints for drug toxicity and efficacy in each patient.

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# Malpractice Insurance — Can the Private Sector Do It?

WHEN ALL THE trappings of the malpractice issue are stripped away a very basic question emerges. Can the private sector provide adequate professional liability insurance to practicing physicians at a reasonable cost? This question points directly to the issue of private versus government medicine with all that this implies for all concerned. If the answer is yes, there is an urgent need to find a way to do it, and soon. If the answer is no, there appear to be two principal alternatives. Physicians can treat patients without adequate insurance and risk their own financial security and that of their families if there is a successful suit. Or, if government assumes some responsibility for a physician's professional liability insurance, government may be expected to exercise some surveillance over his practice. Neither of these alternatives is attractive, nor are they likely to be in the best interests of physicians, or their patients.

Can the private sector do it? At the moment the picture is that of the private sector insurance industry in headlong retreat if not in rout from the field of professional liability insurance for physicians. And already some physicians are unable to get insurance or are unable to pay the premiums. Some of these have begun to practice without insurance, others are retiring from practice prematurely, many are limiting their practice to secure lower rates, and others are not entering private practice at all. All of this means that the private, that is nongovernmental, practice of medicine is in serious trouble—as is the care of unknown hundreds or thousands of patients.

In many ways the present situation seems comparable to one that occurred some 40 years ago. At that time there was a severe economic depression and how to finance medical care itself became a critical issue. There were great pressures for government medicine. Then, the private sector seemed unable or unwilling to cope.